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COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
SAUNDERS, DAVID A	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/719,045
Filing Date: December 07, 2000
Appellant(s): CHAPMAN ET AL.

COZEN O'CONNOR P.C.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed Jan. 26,2007 appealing from the Office action mailed Mar. 29, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect. Appellant incorrectly states that "All amendments have been entered"; however, no amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is deficient. The brief is deficient because the summary uses terminology that differs from that of claim 1, and the summary does not refer to all of the limitations of independent claim 1.

Specifically, the summary of claimed subject matter contained in the brief refers to at least one polymer molecule that is "attached" to the heavy chains of the antibody

fragment. The claim language does not recite "attached" but, rather, recites "covalently linked".

Additionally, the summary of claimed subject matter contained in the brief indicates that the "at least one polymer molecule" is "attached to the heavy chains in a site specific manner on each chain". The summary, however, fails to indicate that the site of attachment on each heavy chain is through "the sulfur atom of a cysteine residue" (see claim 1, lines 4-5 in the Claims Appendix).

Also, the summary of claimed subject matter fails to indicate that the "at least one polymer molecule" is within a "non-disulfide interchain bridge" between the "two antibody heavy chains" (see claim 1, lines 6-7 in the Claims Appendix).

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official

Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

6,025,158	Gonzalez et al.	10-2000
5,436,154	Barbanti et al.	07-1995

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the appellant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the appellant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 12-13 and 15 rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gonzalez et al.

Gonzalez et al teach antibody fragments having an extended circulating half-life by virtue of being conjugated to a high m.w. polymer -- e.g. PEG of 20,000 D or greater. Gonzalez et al disclose embodiments in which two or more Fab, Fab' or Fab'-SH fragments are covalently conjugated to a polymer backbone. The polymer thus links the antibody fragments. See especially col. 35, lines 40-57 and col. 41, lines 41-62. See col. 35, lines 40-57, wherein there is a teaching of "a polymer molecule used to link together two antibody fragments to form a dumbbell-shaped structure." Such a "dumbbell - shaped structure" is consistent with the divalent antibody fragment of instant claim 1.

A preferred site of conjugating the polymer to the antibody fragment is at the hinge region of the latter; see col. 19, lines 56-65 and col. 35, lines 6-13. A most preferred site of attachment therein is a cysteine residue. See, for example, col. 19, lines 56-65. The conjugation of the polymer thereto is achieved by providing a sulfhydryl reactive moiety attached to PEG. See, for example, col. 19, lines 35-55; col. 42, lines 12-18; col. 120, lines 46-52; col. 121, lines 59-64.

In embodiments in which the number of conjugated Fab' fragments, that have been prepared in their Fab'-SH form, is two and the number of polymer members is one, instant claims 1-2 are anticipated or, at the least, obvious as one of numerous embodiments taught within the four corners of the reference.

Regarding claims 3-4, note the teachings regarding the structure of Fab' and Fab'-SH fragments at col. 11, lines 56-64. The structure of further dependent claim 5 would be achieved when one couples the taught Fab'-SH to two activated sites on a polymer to form the dumbbell structure taught at col. 35, lines 45-57.

Regarding claims 6-9, note the polymers taught at col. 41, lines 1-34. Note PEG taught therein at line 9. Note methoxy PEG and m.w. thereof at col. 120, lines 46-52.

Regarding the cross-linkers of instant claim 10, note Gonzalez et al at col. 35, lines 53-57 and col. 41, lines 41-43.

With respect to claim 12, note Gonzalez et al teach conjugation of label/reporter groups at col. 44, line 5-col. 45, line 14.

Regarding claim 13, the IL-8, for which the exemplified antibodies of Gonzalez et al are specific, is a soluble antigen, which is secreted by cells. See col. 1, lines 44-45.

For claim 15, note col. 45, lines 22-25 and col. 96, lines 53-59 for teaching pharmaceutical/therapeutic compositions.

Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al in view of Barbanti et al.

Gonzalez et al have been noted supra for generically teaching the coupling/bridging of Fab, Fab' or Fab'-SH antibody fragments of generic binding specificity, or more particularly of IL-8 binding specificity, to a polymer to extend circulating half-life. Gonzalez et al clearly teach (col. 16, lines 39-46) that the benefits of extended circulating half-life gained by conjugation to the polymer are to be expected "without regard to antigen specificity" of the antibody.

Barbanti et al teach antibodies to TNF-alpha, including fragments of such antibodies (col. 5, lines 44-55), and they teach use thereof for in vivo treatment (col. 5, lines 54-55 and col. 7, lines 6-10). It would have been obvious to conjugate these

antibody fragments of Barbanti et al to PEG in the manner taught by Gonzalez et al, in order to also extend half life of the antibodies. One of skill would have been reasonably motivated to consider both references, because both IL-8 and TNF-alpha are involved in inflammation and because increasing the circulating half-life of an antibody to any mediator of inflammation would have been expected to permit more of the administered antibody to bind the mediator.

(10) Response to Argument

Regarding the 102/103 rejection based upon Gonzalez et al, appellant has offered numerous reasons why the reference does not anticipate or render the instant invention obvious (Brief at pgs 5-9).

Appellant has urged (Brief at pg 5) that "Gonzalez el al does not disclose or suggest a divalent antibody fragment having a polymer molecule covalently linked to a cysteine residue outside of the variable region domain on each heavy chain." Curiously, appellant has subsequently (Brief at pg 5) admitted that "Gonzales et al describes monovalent antibody fragments conjugated to a high molecular weight polymer by a hinge region cysteine"; clearly in this teaching Gonzales et al point to a "hinge region cysteine" which is certainly "outside of the variable region domain". As to this "hinge region cysteine" being on the heavy chain, it is to be noted that Gonzales et al have pointed to attachment of the polymer to the "hinge region of the parental antibody fragment" (col. 19, lines 56-57) and point to the hinge region in the IgG, IgM and IgA isotype heavy chain (col. 19, lines 59-60) and to the engineering of a cysteine residue

into the hinge region (col. 19, lines 62-65). Gonzales et al further exemplify an Fab' expression vector, in which they use "the coding sequence for the human constant IgG1 heavy domain, including the free cysteine in the hinge region that was used to attach the PEG molecule" (col. 120, lines 25-27). Thus Gonzales et al certainly teach attachment of an antibody fragment through a cysteine residue outside of the variable region domain on a heavy chain. In any embodiment wherein two Fab' fragments, that have been prepared in their Fab'-SH form (e.g. as taught at col. 120, lines 17-63), are attached to a polymer, each of these antibody fragments would be covalently linked to the polymer molecule via "a cysteine residue outside of the variable region domain on each heavy chain". As to the divalency of the antibody fragment that appellant urges is not taught by Gonzales et al, appellant should realize that when two monovalent Fab' fragments are attached to a polymer, then divalency results by virtue of the fact that two monovalent fragments have been joined to each other via the polymer. For further consideration of the valency issue appellant is referred to the para. immediately infra.

Appellant has variously argued that Gonzales et al teach "monovalent antibody fragments linked together by polymer molecules" (Brief at pg 5) and that Fab' fragments are monovalent, not divalent" (Brief at pg 8). The examiner is not in error in referring to portions of Gonzales et al that contemplate the conjugation/attachment of two monovalent antibody fragments to the polymer, because this is precisely what appellant has claimed as his invention in claim 1. That is, while claim 1 recites "A divalent antibody fragment" (see claim 1, line 1 in the Claims Appendix), it is only divalent by virtue of the fact that two monovalent fragments have been attached/linked to each

other (via their "cysteine residues located outside of the variable region domain") through a "non-disulfide interchain bridge" that contains the polymer. Thus any teaching of Gonzales et al concerning two monovalent fragments have been attached/ linked to each other via an intervening polymer component is certainly relevant.

Appellant has further argued (pg 5) that "Gonzales et al describes monovalent antibody fragments conjugated to a high molecular weight polymer by a hinge region cysteine, and describes two antibody fragments linked together by polymer molecules (col. 35, lines 45-48), without specifying how and where they are attached." Since this teaching clearly indicates that attachment of the monovalent antibody fragments occurs via "a hinge region cysteine", it is taken that appellant faults Gonzales et al for not specifying how and where they are attached to the polymer. It is not necessary that Gonzales et al teach "where" the antibody fragments are attached to the polymer, since the instant claims lack any recitation as to "where" on the "polymer" the "two antibody heavy chains" are attached/linked. As to "how" the antibody fragments are attached to the polymer, one would of skill would certainly consider that, since Gonzales et al teach that attachment of the monovalent antibody fragments occurs via "a hinge region cysteine", the coupling chemistry concerning attachment through sulfhydryl groups taught at col. 42, lines 12-18 would be applicable.

Regarding anticipation by Gonzalez et al, Appellant has urged (brief at pg 6) that the examiner has improperly argued that the instant invention is within the "4 corners of the reference" and has not shown that the reference meets the standard that "the reference disclose each limitation as arranged in the claim." It is to be noted that

the nature of the reference is such that Gonzales et al have disclosed, in total, a large number of possible kinds of conjugate constructs that vary in the number and type of antibody fragment(s) and that vary in the number of polymer molecules that are to be incorporated into the final conjugate construct. Among the teachings concerning such constructs, there is an explicit teaching of a construct in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure (col. 35, lines 46-47). There is, also, an explicit teaching of how to conjugate an Fab'-SH fragment to PEG (col. 120, line 15-col. 122, line 31).

It is the examiner's position that the disclosure of Gonzales need not ipsis verbis disclose that, when a polymer molecule used to link together two antibody fragments to form a dumbbell-shaped structure, such linkage to each of the two antibody fragments is to be formed by the type of coupling chemistry shown at col. 120, line 15-col. 122, line 31. The disclosure is anticipating for this structure, because it is reasonably considered to disclose all combinations that can result by choosing one the possible kinds of conjugate constructs (with respect to the number and type of antibody fragment(s) and the number of polymer molecules) taught and then choosing one of numerous kinds of coupling/linking chemistry taught. The examiner finds no need for Gonzales et al to have specifically pointed to a particular one of the combinations, since they are all within the scope of what the reference teaches. It is reasonable to take the position that one who is considering what Gonzales et al anticipate would have arrived at the instant invention by listing of all of the possibilities that can result when one chooses from among the various kinds of conjugate constructs (with respect to the number and type

of antibody fragment(s)) and the number of polymer molecules) taught by Gonzales et al, in combination with all of the various kinds of coupling/linking chemistry taught by Gonzales et al. In so doing, one would not have failed to arrive at what appellant is claiming; if one failed to do so, it would be because he had not been reading the reference for its full scope and contents. It is thus not the case, as appellant has urged at page 6 concerning inherency, that one may/might have arrived at the invention. With a proper reading of the reference, one would have necessarily arrived at the instant invention as, at the least, one of many in a listing of all the above noted possibilities. Further, among all of the listed possibilities, one would have been more particularly led to those that involve attachment of the fragments to the polymer via a hinge region cysteine residue, since Gonzales et al teach that a preferred site of conjugating the polymer to the antibody fragment is at the hinge region of the latter (col. 19, lines 56-65 and col. 35, lines 6-13) and that a most preferred site of attachment therein is a cysteine residue. See, for example, col. 19, lines 56-65. Thus what is claimed is inherently within the "4 corners of the reference" even if it is not ipsis verbis disclosed. If these considerations have failed to show that Gonzales et al anticipate, then these considerations are to be taken as showing that Gonzales et al have shown what is claimed to have been obvious, as explained further infra.

In the Argument set forth in the para. spanning brief pages 8-9, appellant has confused the issues by pointing to various irrelevant teachings of Gonzales et al concerning the conjugation of $F(ab')_2$ fragments to the polymer(s). As set forth in the above stated rejection over Gonzales et al, the instantly claimed structure would be

achieved when one couples two of the taught Fab'-SH constructs (col. 120, lines 15-63) to two activated sites on a polymer to form the dumbbell structure taught at col. 35, lines 45-57. The examiner thus has not relied on the teachings of Gonzales et al that pertain to the conjugation of $F(ab')_2$ fragments to the polymer(s). All of appellant's arguments concerning how these teachings would defeat the examiner's position concerning inherency (page 6, last two lines), or how these passages would "teach away" from the claimed invention (page 7, lines 3-5) are thus a mere obfuscating diversion tactic. If these arguments are not a diversion tactic, then they may have been presented because of a confusion as to what is being claimed. As set forth further supra, the examiner considers that, while claim 1 recites "A divalent antibody fragment" (claim 1, line 1 in the Claims Appendix), it is only divalent by virtue of the fact that two monovalent fragments have been attached/linked to each other (via their "cysteine residues located outside of the variable region domain") through a "non-disulfide interchain bridge" that contains the polymer. Thus the teachings of Gonzales et al concerning two monovalent fragments which have been attached/ linked to each other via an intervening polymer component have been considered relevant in the stated rejection. Appellant cannot, therefore, argue that the teachings of Gonzales et al concerning the conjugation of $F(ab')_2$ fragments to the polymer(s) as "teaching away" from the instant invention.

Regarding obviousness over Gonzalez et al, Appellant has urged (pg 7) that Gonzales et al teach away from the instant invention because they teach "making the

divalent antibody fragments using polymer molecules derivatized with "multiple functional groups" to permit the attachment of two or more antibody fragments to the polymer backbone. See column 35, lines 45-57" and because such a teaching of the "use of multiple functional groups suggests multiple attachment locations on each chain of the antibody fragment." The examiner finds it curious that appellant has ignored the clear teaching therein that "In one embodiment, a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure" (col. 35, lines 45-48). It is clear in this context that the recited "antibody fragments" can be any of Fab, Fab' and Fab'-SH (see numerous preceding teachings). Appellant is referred to the further above para. in which the examiner has indicated that it is proper for the examiner to consider such monovalent fragments of Gonzalez et al. Clearly the number of these fragments (2) and the number of polymers (1) in this "dumbbell-shaped structure" are equal to the number of heavy chains and the number of polymer molecules recited in instant claim 1. The examiner thus fails to see how column 35, lines 45-57, when read for all of their disclosed embodiments, would teach away from the invention of instant claim 1.

Regarding obviousness over Gonzales et al, Appellant has further urged (pg 7) that Gonzales et al teach away from the instant invention because they teach "making the divalent antibody fragments using polymer molecules derivatized with "multiple functional groups" to permit the attachment of two or more antibody fragments to the polymer backbone. See column 35, lines 45-57. The use of multiple functional groups suggests multiple attachment locations on each chain of the antibody fragment. The

examiner fails to see how this teaching of "multiple functional groups" suggests multiple attachment locations on each chain of the antibody fragment, because the "multiple functional groups" are present on the polymer molecules for the purpose of attaching of multiple antibody fragments to the polymer, not for the purpose of attaching the antibody fragment at multiple points, along each of its chains, to the polymer. See the taught embodiment of "rosette" shaped conjugates at col. 35, lines 48-57.

Appellant has further urged (brief at pg 7) that "Indeed, Gonzales et al lists a variety of crosslinking sites on the antibody fragments that can be used, e.g., N-terminal amino groups and epsilon amino groups found on lysine residues, amino groups, imino groups, carboxyl groups, sulfhydryl groups, hydroxyl groups, and other hydrophilic groups (See column 41, lines 63-57)". These teachings, however, do not buttress appellant's assertion that "multiple functional groups" suggests multiple attachment locations on each chain of the antibody fragment". The examiner finds that the full para. from col. 41, line 63-col. 42, line 24, points to multiple different ways of attaching the polymer to the antibody fragment. Each kind of group on the antibody fragment (e.g. NH, SH) is coupled to the polymer by a different kind of coupling chemistry, as shown by the teachings therein of the different ways in which PEG is to be derivatized. The examiner's position is further buttressed by the fact that, though Gonzales et al have taught coupling to diverse kinds of groups on the antibody fragment at col. 41, line 63-col.42, line 24, Gonzales et al show coupling to only one such group (i.e. an SH group of a cysteine in the hinge region) when they conjugated an Fab'-SH fragment to PEG (col. 120, line 15-col. 132, line 31).

Appellant has then urged that the examiner has not made a prima facia case of obviousness because there is no suggestion within the reference to make the combination, and that the examiner could not have arrived at the instant invention without hindsight (brief at pgs 7-9). The examiner considers that no explicit statement that directly suggests the divalent antibody fragment of instant claim 1 is required for obviousness. What Gonzales et al have disclosed, in total, is a large number of possible kinds of conjugate constructs that vary in the number and type of antibody fragment(s) and that vary in the number of polymer molecules that are to be incorporated into the final conjugate construct. Appellant certainly cannot deny that that there is an explicit teaching of forming a construct in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure" (col. 35, lines 46-47). Appellant certainly cannot deny that there is an explicit teaching of how to conjugate an Fab'-SH fragment to derivatized PEG (col. 120, line 15-col. 122, line 31). The only step that one of ordinary skill in the art would need to take is to realize that, when a polymer molecule used to link together two antibody fragments to form a dumbbell-shaped structure, such linkage to each of the two antibody fragments could be formed by the type of coupling chemistry shown at col. 120, line 15-col. 122, line 31. This is certainly within the ordinary skill of one in the art, since they only insight required would be for one to select one of the possible combinations that can result by choosing one the possible kinds of conjugate constructs (with respect to the number and type of antibody fragment(s) and the number of polymer molecules) taught by Gonzales et al and then choosing one of numerous kinds of coupling/linking chemistry taught by Gonzales et al.

The examiner finds no need for Gonzales et al to have specifically pointed to a particular one of the combinations, or to have provided any particular motivation toward one of these, since they are all within the scope and contents of the prior art. There is certainly no hindsight involved, because one would necessarily have listed what is encompassed by instant claim one, had one made a listing of all of the possibilities that can result when one chooses from among the numerous kinds of conjugate constructs (with respect to the number and type of antibody fragment(s)) and the number of polymer molecules) taught by Gonzales et al, in combination with all of the numerous kinds of coupling/linking chemistry taught by Gonzales et al. Further, as noted supra under anticipation, among all of the listed possibilities, one would have been more particularly led to those that involve attachment of the fragments to the polymer via a hinge region cysteine residue. For one to have failed to arrive at what appellant is claiming would represent less than ordinary skill in the art.

The only manner in which appellant has been able to argue against obviousness is by urging that Gonzales et al teach away from the invention. In every case, as noted supra by the examiner, appellant has urged that Gonzales et al teach something that they do not teach, or has focused upon one of the embodiments taught by Gonzalez et al that is outside of what is relevant to the instantly claimed invention.

Regarding the 103 rejection based upon Gonzalez et al in view of Barbanti et al, appellant has offered numerous reasons why the references are not combinable (Brief at pgs 9-10). Appellant has first argued (pg 9) that "The Office relies upon column 16,

lines 39-46, of Gonzalez et al for allegedly teaching that the benefits of extended circulating half-life gained by conjugation to a polymer were to be expected without regard to antigen specificity." Apparently, appellant would like the BPAI to consider that the examiner has misread the reference by stating that Gonzales et al "allegedly" teach something that they do not teach. The examiner finds these urgings devoid of merit, because there is no ambiguity in what Gonzales et al teach; they clearly teach that "the beneficial aspects of the invention extend to antibody fragments without regard to antigen specificity" (col. 16, lines 39-40). There have thus been no allegations concerning the teachings of Gonzales et al regarding the expected benefits of PEGylation, regardless of antigen specificity.

Appellant has then argued (pgs 9-10) that the examiner has misquoted Gonzales et al at Col. 1, lines 29-32, by virtue of having argued (action of 3/29/04 at pg 4) that "Gonzales et al teach that "PEGlaytion" of antibody fragments has been shown to extend serum half-life levels to useful levels" at col. 1, lines 29-32; while what Gonzalez et al actually teach therein "...PEGylation has not been shown to extend serum half-life to useful levels." Irrespective of this misquote, the teachings at col. 1, lines 29-32 are to be taken merely as a review of the state of the art, prior to the time that Gonzalez et al filed. Appellant cannot deny the clear teachings of Gonzales et al that indicated that they have shown how PEGylation is useful for extending serum half-life of antibody fragments (col. 16, lines 39-45) and have exemplified such extended serum half life

(Section (II)(5)(X) at col. 127, line 61+).

Appellant has then argued (pg 10) that the examiner has misquoted and misinterpreted Gonzales et al as teaching that "antibody fragments, regardless of their antigen specificity, do not have sufficient serum half-life to be useful". Irrespective of whether or not Gonzales provided such a teaching, and irrespective of whether or not Barbanti et al provided any teaching that their anti-TNF-alpha antibody fragments did not have a sufficient serum half-life, it is considered that that one of ordinary skill would have been motivated to extend the serum half life of an antibody fragment, by the method of Gonzales et al. Even if that particular antibody fragment had been taught as having some degree of useful therapeutic effect in its naked (non-PEGylated) form, it would have only been a person having less than ordinary skill in the art who would have not been motivated to extend the half-life of an antibody that is being administered for the purpose of neutralizing an inflammatory molecule such as TNF-alpha.

Appellant has then argued (pg 10) that the examiner has committed "two glaring flaws" in arguing that motivation is implicit from the Barbanti et al reference per se. The first of these flaws is stated as: "First, Barbanti et al gives absolutely no suggestion that serum half-life is considered to be a problem, or that longer serum half-lives are desired." The examiner does not consider it necessary for Barbanti et al to have provided any such explicit teachings. One who knew also of the teachings of Gonzales et al concerning the extension of serum half-life by means of PEGylation, would have been motivated to make the modifications taught therein to the anti-TNF-alpha antibody of Barbanti et al. It is entirely unreasonable for appellant to consider that there must

have been an explicit teaching in Barbanti et al concerning an inadequate serum half life, because the filing date and the issue date of Barbanti et al considerably pre-date the filing date and the issue date of Gonzales et al. It cannot therefore be expected that Barbanti et al would have had the clairvoyance to realize the desirability of increasing serum half life of antibody fragments, as taught by Gonzales et al. It is only a person having less than ordinary skill in the art who, when given the teachings of Barbanti et al and Gonzales et al, would not have been motivated to apply the advances in the art taught by Gonzales et al, for the purpose of extending serum half-life of antibody fragments taught by Barbanti et al.

The second of these flaws is stated as: "the Office is focusing upon a single treatment. Barbanti et al, however, clearly contemplates multiple administrations over time (see column 22, lines 39-44)." The examiner does not see how Barbanti et al therein teach "multiple administrations over time". What they teach is that the "antibody is administered at different times" in a "set of experiments" in which "the neutralizing activity in vivo of the anti-TNF-alpha monoclonal antibody over time is evaluated." The natural reading of these teachings and of the results presented in Table 5, would be that in this "set of experiments" different groups of mice were administered the monoclonal antibody "at different times". Barbanti et al, at col. 19, lines 6-21, give this interpretation to such a "set of experiments". Irrespective of what col. 22, lines 39-44 may or may not teach, it is to be noted that Barbanti et al teach that there can be "Single or multiple

adminstrations of the composition..." (col. 7, lines 22-23). Thus the examiner considers that, at the least, there was no second "glaring flaw" in the rejection of record.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

David A. Saunders 5/11/07

DAVID A. SAUNDERS
PRIMARY EXAMINER

Conferees:

Christina Chan (SPE, Art Unit 1644)

Larry Helms (SPE, Art Unit 1643)

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER